[Jacob]

July 16, 1955

Dear Francois:

Thank you very much for sending us the mss. of your several papers that have to do with K-12 genetics. We have been somewhat remiss about our correspondence generally, for the usual reasons; Esther is especially sorry not to have finished a half-completed letter (commenting on the Lp transduction paper) that has been sitting in her desk for weeks. She sends her apologies, along with a query whether you want to return any comment on the letter she sent you last summer from Woods Hole (on erotic induction). I will confine myself to the recent notes on "mechanism of recombination". It will perhaps clarify my own position to copy a diagram from a review that was part of the Oak Ridge symposium (and I wish the level of our secretarial service made it possible for me to return the favor of exchanging mss., but this was rather a long paper)— which should have been in print months ago, but isn't.

For the known mechanisms of recombination in bacteria, there should be perhaps two criteria for distinguishing sex from transduction. Like any other, the categories of this classification are not necessarily sharply delineated, and having reached the current stage of enlightenment on genetic recombination, there may not be too much point in fussing over what is or is not "sex"; this was not so true ten years ago when the transduction theory for the pneumococcus transformation had not been generally applied and related to other recombination mechanisms.

The criteria just mentioned have been (in my own mind): 1) the interaction of intact cells (contra subcellular [i.e. filtrable] vectors) and 2) the initial transmission of a whole [or substantially whole— cf. heterogametic sex determination] genome by both gametes. Criterion 1), having been somewhat confused by the relationships of F seems no longer controversial, if I correctly interpret your and Hayes' usage of "conjugation" or "zygote". Criterion 2) has been the most vexatious problem ever since the "aberrant heterozygotes" were first discovered to be hemizygous for certain genes, notably Mal and S (and later found to include Lp and some Gal's).

Unfortunately (it is my own conclusion that) data on viable haploid recombinants cannot distinguish between two explanations of the loss of genetic material that is revealed in the heterozygotes and in F polarity effect generally; 3) does this segmental loss occur prior to the formation of the "zygote" or 4) subsequently; and 5) is the loss variable or constant. Concerning 3)/4) the study of diploids has given results that favor 4) almost unambiguously (see Nelson and JL, PNAS, 40:415, 1954) so I won't repeat the argument. Similar studies have answered 5) equally definitely: the region that is subject to elimination is precisely defined— it always includes the markers Mal_1; S; Lp; Gal_1, Gal_2 etc; it never includes any of the other markers that have been studied, such as Lac, for example. Most strikingly, Gal_2 is regularly heterozygous, while the closely linked Lp, Gal_1 etc., are invariably hemizygous. If I had ever seen a diploid that was hemizygous for Lac but heterozygous for Mal (the converse of the usual situation), I would have to adopt a different view Since you have had the Het stock (ask Jacques anyhow) for some time now, I would urge you to verify some of these points yourself; we are still working on some of the details of the Gal segment ourselves. But I have not been able to reconcile these findings with any other tolerable scheme but that the breakage points are invariable, and that the breakage (or at least the loss of the distal segments) is postzygotic.

This scheme is compatible with any data from pairing analysis, whether cytological or inferred from mechanical shearing: I think it would have to be since the latter tests could not separate the deficiencies that may arise before from those after the zygote is formed. Although relatively few loci are known to be eliminated, the effects spread much further since any marker linked to a deletion will also be lost (in a haplo-lethal nucleus) unless separated by crossing-over. Thus the gradient that we had observed in the "transmission" of the markers [to recombinants not necessarily to the zygote as you imply] might be explained by a deletion which is distal to TL, for which we so far have no included markers.

As to your own experiments, I am puzzled by one point of the theory. The αV_1 plateau for Az and T5 at 20 minutes suggests that the "0" region of each gamete had been transmitted by this time. The Gal region, and the Lac, would evidently only begin to come in afterwards. Are you postulating that these markers are on a single chromosome the same as the TL? If so, then you must ascribe the fractional transmission (e.g. Az without Lac) to the breakage by the mechanical treatment (Waring blendor?), and the normal course of events would have been the transmission of the whole genome. Since my own diploid experiments have not included artificial coitus interruptus, there is not necessarily any inconsistency between the regularity of elimination in normal crosses and the variability that you infer for these conditions. However, I may have misread your thinking on this question and hope you will enlighten us. To verify this conclusion, I would think it would be necessary to isolate some unreduced aneuploids, which would then perhaps be comparable to the Lac-/df Mal+/- that I have never seen otherwise. [Hayes and Skaar have intimated, respectively, that they may have fragmentation of a similar sort in crosses of T-1 infected K-12, and in strain B x K-12, for either of which more evidence is needed. It would be a clever thing to induce transduction intracellularly by fragmenting the male gamete, and it suggests what ought to be tried with higher forms. In passing, have you ever heard the outcome of similar attempts by Luria to obtain partial "injections" of T1 or T5 by changing the ionic environment?]

Until the intermediate stage can be isolated and characterized, I would reserve judgment on whether you have partial fertilizations, or whether you have modified the chromosome pairing pattern (as you already suggest as the effect of UV) so as to influence the probability of crossing ever between a fixed deletion and the markers you are following. I have been hoping to develop the technical possibility of mating Hfr x F- diploids (for conjugal pairs) in hopes of better defining the content of the Hfr gamete, but so far this is not nearly feasible.

Notwithstanding the differences in outlook, we appreciate your keeping us informed of your findings and only regret the barrier of distance that prevents the easy synthesis (or compromise?) of our conclusions. Have you ever thought of spending a year in the U.S.? If there were any possibility of your taking the time, I am sure you would have no difficulty in obtaining a subsidy for your passage, perhaps from Fulbright or Rockefeller; given that, and some time for preparation, I am sure we could make it financially comfortable. Our lab. is due to be somewhat improved also, and we would do our best to make you at home. We might even speak French in the lab— but that might send you back to Paris.

I hope you will forgive the orientation of this letter; the presentation of my own views does not mean that I insist upon them, but this form seemed the most convenient technique to expose them to your comment. I have been working on recombination for almost 10 years, too long a time I think, and it would be a great comfort to be able to adopt any theory that would reconcile the excess of facts.

With best regards to Elie and Jacques and Alain Bussard,

Yours sincerely

Professor of Genetics

P.S. What do you make of Fredericq's menages a trois-- the crosses involving colicin E. On kinetic grounds, such ~~triparent~~ triparental combinations are incredible, whatever hypothesis of mechanism. But Dr. Bernstein here did some experiments (just before returning to England) with colicin F (probably same locus) whose results agreed with Fredericq's, so that must be accepted at face value. Nor could Bernstein find any high frequency of transmission of Ckf^r (colicin F resistance) in mixtures without selecting for other recombinants. Have you done or heard any more on this? The possibilities of a trivial explanation are not exhausted, but it is most puzzling.

John

RECOMBINATION IN BACTERIA

	Heterokaryosis	Sex (karyogamy)	Transduction	Infection —lysogenic conversion—	
Unit	nucleus	nucleus	chromosome fragment	provirus	
Agency	cytogamy (—copulation or conjugation→)	cytogamy and karyogamy	DNA	Virus inclusion	Virus "inclusion"
Occurrence	Streptomyces [Bradley & Lederberg]	K-12 and other E. coli	pneumoc. Hemophilus Neisseria	Salmonella Shigella E. coli P1	
				— E. coli Gal/lambda—	
				—E. coli PY /lambda—	
				Salmonella Iseki Corynebact. B. magath...	

(modified from JCCP Suppl. 2 1955)

lysogeny in general